Successful Infusion of Obinutuzumab by Desensitization: A Case of Anaphylactic Shock During Desensitization

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Obinutuzumab is a humanized, type II, anti–cluster of differentiation 20 (CD20) monoclonal antibody that binds to CD20 on B cells and causes cell death by activating intracellular apoptosis pathways and the complement system [1]. It was shown to confer survival advantages in a recent comparison with rituximab for the treatment of chronic lymphoblastic leukemia, small lymphocytic leukemia with comorbidities, and relapsed or refractory follicular lymphoma [2]. The common adverse effects of obinutuzumab are infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders [1]. Infusion reactions occur in approximately 10% of patients receiving obinutuzumab and can be fatal in severe forms, such as anaphylaxis [1]. We present an 18-step intravenous desensitization protocol for obinutuzumab that was successfully carried out in a general ward setting.

A 71-year-old man with a history of B-cell chronic lymphoblastic leukemia was admitted for chemotherapy. He had never received chemotherapeutic agents and denied having any underlying disease history, including allergies. His hematologist administered obinutuzumab/chlorambucil. A total of 1000 mg of obinutuzumab was planned to be administered on days 1, 8, and 15 with premedication; obinutuzuamb was planned at 100 mg on day 1 and 900 mg on day 2 in the first cycle in order to prevent an infusion reaction, which is common during the initial administration. Despite premedication with oral chlorpheniramine (4 mg), oral dexamethasone (20 mg), and oral acetaminophen (650 mg), the patient experienced chest and abdominal discomfort and sore throat 1 hour after the initiation of the obinutuzumab infusion (100 mL of solution at 1 mg/mL). Oxygen saturation decreased to 85%. The infusion was discontinued immediately, and the symptoms improved after administration of oxygen and intravenous chlorpheniramine. Once the symptoms had completely resolved, obinutuzumab was resumed on the same day with a 12-step desensitization protocol (Supplementary table) and additional premedication including chlorpheniramine (4 mg), methylprednisolone (40 mg), and propacetamol (1 g). Infusion was initiated with a solution of 1 mg/mL at a rate of 0.1 mL/h (0.25 mg/15 min) and doubled every 15 minutes using a syringe pump (Injectomat Agilia) based on our institutional protocol for chemotherapeutic agents [3]. However, when the rate reached 0.4 mL/h, the patient developed a breakthrough reaction (BTR) characterized by high fever, dyspnea, chest discomfort, and stridor. Oxygen saturation decreased instantly to 85% on room air, and the pulse was not palpable. A diagnosis of anaphylactic shock was confirmed, and the symptoms were reversed with a massive intravenous infusion of normal saline and an intramuscular epinephrine injection (0.3 mg).

Two weeks after recovery, a skin test was carried out with obinutuzumab 0.1 mg/mL and 1 mg/mL, although the results were not positive for histamine or obinutuzumab. In order to resume obinutuzumab, the desensitization protocol was modified by mitigating the increments of the rate between steps to 1.6 times per 15 minutes and prolonging the total number of steps to 18. One hour before initiating desensitization, the patient received premedication with ketotifen (1.38 mg), famotidine (20 mg), montelukast (10 mg), and dexamethasone (20 mg). Cycle 1 was completed with 2 bags of obinutuzumab (100 mg in 100 mL of 0.9% normal saline [1 mg/mL] and 900 mg in 250 mL of 0.9% normal saline [3.6 mg/mL] based on the package insert) serially administered in an 18-step desensitization protocol (Table). The first solution was successfully administered without BTR in 6.3 hours. The remaining 900 mg of obinutuzumab (3.6 mg/mL) was followed by the same incremental rate for continued desensitization. Following successful initial chemotherapy, desensitization was repeated for administration of obinutuzumab, with no BTR.

Various systems can be affected by the main chemotherapy-related hypersensitivity reactions, which include flushing, chest pain, dyspnea, nausea/vomiting, and disorientation. The reactions may be very severe and even fatal and can be induced by various chemotherapeutic agents [4]. Although more chemotherapeutic options are currently available, the survival benefits of the next best option may not match those of the first choice. When this is the case, physicians can consider desensitization to the culprit agent despite hypersensitivity reactions, instead of switching to other options.

Desensitization, which is performed by sequentially increasing doses over multiple steps to attain immunologic tolerance, often proves to be a safe option for people who experience severe reactions to their chemotherapy agent [5]. While a 3-bag, 12-step desensitization protocol has been widely used [6], additional work is necessary to ensure serial dilutions of the chemotherapeutic solution. In our institution, a rapid nondilution desensitization protocol has been successfully adopted for the reintroduction of chemotherapy agents associated with hypersensitivity reactions [3]. This protocol is administered with the help of a syringe pump, which enables precise delivery of very small amounts (0.1 mL/h) without dilutions. In the case we report, desensitization was carried out using 2 sets, since the package insert of obinutuzumab recommended 2 different concentrations for infusion.

Managing BTR during the desensitization process is important for a successful outcome. If BTR occurs during the

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Table. Eighteen-Step Obinutuzumab Desensitization Protocol[a]

Concentration, mg/mL	Step	Rate, mL/h	Time, min	Dose Administered, mg	Volume Administered, mL	Cumulative Dose, mg
1.0	1	0.1	15	0.024	0.025	0.024
	2	0.2	15	0.0481	0.05	0.0721
	3	0.3	15	0.0721	0.08	0.1442
	4	0.5	15	0.1202	0.13	0.2644
	5	0.8	15	0.1923	0.2	0.4567
	6	1.3	15	0.3125	0.33	0.5048
	7	2.1	15	0.5048	0.5	1.274
	8	3.4	15	0.8173	0.85	2.0913
	9	5.5	15	1.3221	1.38	3.4135
	10	8.9	15	2.1394	2.23	5.5529
	11	14.4	15	3.4615	3.6	9.0144
	12	23.3	15	5.601	5.83	14.6514
	13	37.8	15	9.0865	9.45	23.7019
	14	61	15	14.7356	15.3	38.4375
	15	99	15	23.7981	24.8	62.2356
	16	160	14.7	37.7644	39.3	100
3.6	17	80	15	62.9371	20	162.9371
	18	130	122.8	837.0629	266	1000

[a]The 1.0-mg/mL solution used for steps 1-16 was prepared by reconstituting obinutuzumab 100 mg in 100 mL of 0.9% normal saline; the 3.6 mg/mL solution used for steps 17 and 18 was prepared by reconstituting obinutuzumab 900 mg in 250 mL of 0.9% normal saline.

desensitization process, it is recommended to reduce the initial dose, increase the time interval, or add intermediate steps to decrease the increments in order to attain tolerance [7]. In this case, BTR occurred during the initial desensitization process, but were successfully managed by mitigating the increments between steps, since lowering the rate of the initial step to below 0.1 mL/h was not feasible in our protocol.

Although severe hypersensitivity of obinutuzumab has been reported in cynomolgus monkeys, in which immune complex deposits were observed in tissue [8], there are currently no reports of true immunologic reactions being more likely than infusion reactions in humans. In the case we report, a skin test was performed but could not be interpreted owing to decreased skin reactivity. Therefore, it was difficult to determine whether an IgE-mediated mechanism played a role or not. Isabwe et al [9] previously reported the safety and effectiveness of desensitization protocols for 16 monoclonal antibodies, including 2 cases of obinutuzumab hypersensitivity that were characterized by a remarkable increase in IL-6 during desensitization, thus reflecting cytokine release as the underlying endotype. However, regardless of the mechanism, the general consensus for severe reactions is to discontinue the culprit medicine, and it is not usually recommended to retry desensitization for a case experiencing anaphylactic shock despite desensitization. Desensitization can still reduce the probability and severity of BTR if performed on an individual basis and applied with caution in selected cases.

In summary, we report successful reintroduction of obinutuzumab in a patient who presented with anaphylaxis during initial desensitization but who eventually tolerated the drug following a mitigated desensitization protocol with 1.6-fold increments between steps.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

The data in this study were presented in poster form at a conference of The Korean Association of Internal Medicine.

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